REMARKS

Following this amendment claims 1-6, 9-18, 29-31, 35-36 and 39-41 will be pending. Support for the claims as amended may be found on page 7, lines 15-17, the examples and throughout the application as originally filed. No new matter is added as a result of this amendment. Applicants believe the current amended claims and remarks below address the Examiner's remaining concerns.

Summary of the Office Action

Claims 1, 4-32 and 35-39 were rejected under 35 U.S.C. §112, 2nd ¶. Claims 1-32 and 35-39 were rejected under 35 U.S.C. §112, 1st ¶. Claims 1-9, 12-22, 25-28, 31, and 38 were rejected under 35. U.S.C. § 103(a) as being unpatentable over Laustsen (U.S. Patent 6,080,564) in view of Larsen (WO 95/29999) and Heinsohn (U.S. Patent 5,215,908). Claims 10, 11, 23, 24, 29, 30, 32, and 35-37 were rejected under 35. U.S.C. § 103(a) as being unpatentable over Laustsen in view of Larsen and Heinsohn and further in view of Ward (*Biotechnol* 8:435-440, (1990)).

Objections

The Applicant submits that the USPTO's objection to claim 7 is obviated as claim 7 has been cancelled.

35 U.S.C. § 112 ¶ 2

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1, 4-32 and 35-39 were rejected in sections 2-4, under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. In particular, in section 2 on pages 2-3 of the Office Action, the USPTO stated "it was unclear as to whether the desired polypeptide maintains activity during and/or after treatment at a pH <2.0." Applicant respectfully submits that claim 1 (prior to its amendment herein) was

definite insofar as it readily apprised persons skilled in the art of the metes and bounds of the claimed invention. Applicant appreciates the Examiner's suggestions and, in the interest of advancing prosecution, Applicant has amended claim 1 to indicate that chymosin maintains "at least partial enzymatic activity." Additionally, claim 7 has been deleted. Applicant respectfully requests the rejections be withdrawn.

35 U.S.C. § 112 ¶ 1

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

On pages 3-4 of the Office Action, section 5, claim 32 was rejected. Claim 32 has been cancelled. On pages 4-6 of the Office Action, section 6, claims 1-32 and 35-39 were rejected for the reasons of record. In the previous Office Action, the USPTO stated claims 1-32 were rejected because "while being enabling for a method of preparing chymosin with reduced undesired glucoamylase, peptidase, amylase, cellulase, phosphatase, and protease activities by treating a non-acidophilic cell medium comprising said enzymes at a pH of 1.6 to 1.8 for a time sufficient to reduce glucoamylase, peptidase, amylase, cellulase, phosphatase and protease enzyme activities as compared to untreated glucoamylase, peptidase, amylase, cellulase, phosphatase, and protease enzymes, [it] does not reasonably provide enablement for a method of producing *any* desired polypeptide having reduced content of *any* enzymatic side activities by treating *any* medium with *any* pH of less than 2.0 as encompassed by the claims." (Emphasis in the original.) (*See*, Office Action dated April 9, 2002, page 5). While Applicant maintains that the specification indicates that the scope of enablement is broader than stated in the Office Action (as detailed in the Amendment filed on October 9, 2002), Applicant has amended claim 1 to incorporate the subject matter which the Examiner stated is enabled. However, Applicant directs the USPTO's attention to the broader scope of the invention disclosed throughout the application regarding each feature of the claimed invention. For instance, the pH values specifically tested include at least: pH of 1.15, 1.30, 1.48 and 1.61 (Example 1); pH of 1.6, 1.7 and

1.8 (Example 2); and a pH of 1.7 (Example 3).

Applicant respectfully requests the rejection be withdrawn.

35 U.S.C. §103(a)

> (a) A patent may not be obtained through the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

On pages 7-9, section 12 of the Office Action, the USPTO purports that claims 1-9, 12-22, 25-28, 31 and 38 are obvious over Laustsen (U.S. Patent 6,080,564) in view of Larsen (WO 95/29999) and Heinsohn (U.S. Patent 5,215,908) for the reasons of record. The USPTO stated that Applicant's arguments and declaration were not persuasive in this regard. The USPTO maintains that Larsen teaches that "a pH as low as 0.5 can be used to convert inactive chymosin to an active form" while Laustsen teaches "inactivating undesired enzyme activities (e.g. protease, amylase and cellulase) by treatment with low pH" and "a methods of inactivating undesired enzyme activities in the presence of a desired enzyme." Office Action, p. 8. The USPTO then combines the references and states that "[o]ne would have a reasonable expectation of success for treating an *Aspergillus* medium comprising a recombinantly produced chymosin with a pH as low as 0.5 in order to remove contaminating protease, amylase and cellulase enzyme activities." Office Action, pp. 8-9. Further, the USPTO stated that a combination of references can not be overcome by attacking the references individually. Applicant respectfully points out the combination of references was discussed in her October 9th Amendment and failings in an individual reference for the points cited by the USPTO may render a combination inoperative. The USPTO alleged that "[o]ne would have been motivated to practice the method of Laustsen using an Aspergillus host cell expressing inactive chymosin and adjusting the pH of the medium to 0.5 in order to remove contaminating protease, amylase, and cellulase enzyme activities while holding the pH as acidic as possible for a desired polypeptide as taught by Laustsen, to convert the inactive chymosin to active chymosin as taught by Larsen, and to stop cell

growth and fermentation as taught by Heinsohn, all in a single step." (*See*, Office Action dated April 9, 2002, page 9).

Applicant claims an invention directed to a method of providing a polypeptide preparation having a content of undesired enzymatic side activities at such a level that they do not restrict the applicability of said polypeptide preparation for its intended purpose, comprising providing a medium having a pH of 2.0 or higher that comprises chymosin and in addition at least one undesired enzymatic side activity selected from glucoamylase, peptidase, amylase, cellulase, phosphatase or protease, and subjecting said medium to a pH between about 1.5 to about 1.9 for a period of time that is sufficient to at least partially inactivate said at least one undesired enzymatic side activity while maintaining at least partial enzymatic activity of said chymosin.

First, it is respectfully submitted that the "initial burden of establishing a basis for denying patentability to a claimed invention rests upon the USPTO." (*In re Fines*, 5 U.S.P.Q. 2d 1596 (Fed. Cir. 1988)). As stated by the Federal Circuit, "a proper analysis under 35 U.S.C. § 103 requires, *inter alia*, consideration of two factors: (1) whether the prior art would have suggested to those of ordinary skill in the art that they should make the claimed composition or device, or carry out the claimed process; and (2) whether the prior art would also have revealed that in so making or carrying out, those of ordinary skill would have a reasonable expectation of success." *In re Vaeck*, 947 F.2d 488, 493 (Fed. Cir. 1991). In addition, the prior art reference(s) must teach or suggest all of the claim limitations. The teaching or suggestion to combine and the reasonable expectation of success must both be found in the prior art, and not in Applicant's disclosure. *Id* at 493. *See also* M.P.E.P. § 2142. The Federal Circuit recently explained that "...the best defense against the subtle but powerful attraction of hindsight - based obviousness analysis is rigorous application of the requirement for a showing of the teaching or motivation to combine prior art references." (*In re Lee*, 61 U.S.P.Q. 2d 1430, 1433 (Fed Cir. 2002), quoting from *In re Dembiczak*, 50 U.S.P.Q. 2d 1614, 1617 (Fed. Cir. 1999)).

Applicant further notes that the claimed invention now recites the desired polypeptide includes chymosin while the undesired activity is selected from glucoamylase, peptidase, amylase, cellulase, phosphatase or protease. Further, the

claimed invention now recites the medium is subjected to a pH range between about 1.5 to about 1.9. Applicant submits that in addition to the recitation of desired polypeptide and undesired side activities, the art cited by the USPTO fails to recognize or teach the range of the claimed invention. Indeed, each of the references individually and in combination teach away from the claimed pH range. Laustsen's inactivation occurred at pH 3.5 and 10.7 as discussed in examples 4 and 5 respectively. The use of the divergent pH's by Laustsen does not necessarily direct one to inactivate amylase activity at the lower pH taught by Laustsen. In fact, the teachings of Laustsen are likely to suggest to a person skilled in the art that a pH of 10.7 or a pH between 3.5 and 10.7 should be used, thereby teaching against the claimed invention. Additionally, even if one were to choose the lower pH used in Laustsen, there is no suggestion that a pH between about 1.5 and about 1.9 should or could be used without detrimental effects on the desired enzyme activity.

Alternatively, Heinsohn which relates to chromatographic purification of chymosin from unspecified enzymes and other impurities, discusses an acid pre-treatment at pH 2-3 before chromatography but is really directed toward purification and not inactivation of undesired side activities. Further, Heinsohn does not provide guidance to use a range between about 1.5 and 1.9 for any purpose, much less to inactivate undesired side activities while maintaining at least partial activity of the desired polypeptide. Similarly, Larsen teaches a process for separating milk clotting to obtain chymosin and the USPTO states Larsen teaches "that following the extraction process the pH of the extract is adjusted to as low as 0.5 using inorganic or organic acids in order to convert the inactive chymosin to active form." (*See*, Office Action dated April 9, 2002, page 8). Larsen however was directed at the activation of endopeptidases not the elimination of undesired enzymes while maintaining at least partial activity of the desired polypeptide activity. Given the wide range of pH's used in the three references, one would certainly not be motivated to combine the references to obtain the claimed invention which relates to providing a desired polypeptide while eliminating specific undesired activities at a specific pH range.

Prior art references in combination do not make an invention obvious unless something in the prior references would suggest the advantage to be derived from

combining their teachings. *In re Sernaker*, 217 U.S.P.Q. 1, 6 (Fed. Cir. 1983). This is particularly true given the recitation of the claimed pH range. In the present case, the USPTO has done no more than find the separate elements of the claimed invention in disparate pieces of prior art and argue that broad disclosures, which would require specific selection and experimentation to achieve the Applicant's claimed invention, render the claimed invention obvious.

The rejection is respectfully traversed at least for the above reasons.

On page 9, section 8 of the Office Action the USPTO rejected claims 10, 11, 23, 24, 29, 30, 32, 35-37 and 39 as obvious over Laustsen in view of Larsen and Heinsohn and further in view of Ward (*Biotechnol* 8:435-440, May 1990). Applicant reasserts her statements above regarding the Larsen, Laustsen and Heinsohn references, and discusses the Ward reference.

Initially, Applicant points out, as the Examiner has noted, that the Ward reference does not suggest using a pH below 2.0 and therefore one must combine Ward with the above references in order to achieve the desired pH range. As the above references do not provide guidance for the claimed pH range, their combination with Ward which is directed toward the production of chymosin using a fusion protein to increase production, fails to render the claimed invention obvious.

The fact that a claimed product is within a broad field of the prior art and one might arrive at it by selecting specific items and conditions, does not render the product obvious in the absence of some directions or reasons in the prior art for making such selections. (*Ex parte Kuhn*, 132 U.S.P.Q. 359 (Pat. & Tr. Office Bd. App.)(1961)). Prior art references in combination do not make an invention obvious unless something in the prior references would suggest the advantage to be derived from combining their teachings. *In re Sernaker*, 217 U.S.P.Q. 1, 6 (Fed. Cir. 1983). In the present case, the USPTO has done no more than find the separate elements of the Applicant's claimed invention in selected references and argue that broad disclosures, which would require specific selection and experimentation to achieve the current invention, render the claimed invention obvious.

A combination may be patentable whether it be composed of elements all new, partly new or all old. *Rosemont, Inc. v. Beckman Instruments, Inc.*, 221 U.S.P.Q. 1, 7

(Fed. Cir. 1984). There must be something in the prior art as a whole to suggest the desirability, and thus the obviousness, of making the combination. *Lindemann v. Maschinenfabrik GMBH v. American Hoist & Derrick Co.*, 221 U.S.P.Q. 481, 488 (Fed. Cir. 1984). *Interconnect Planning Corporation v. Feil, et al.*, 227 U.S.P.Q. 543, 551 (Fed. Cir. 1985). In the present case there is no such motivation. One cannot pick and choose among individual parts of assorted references to form a mosaic to recreate a facsimile of the claimed invention. *AKZO N.V. v. International Trade Commission*, 1 U.S.P.Q.2d 1241, 1246 (Fed. Cir. 1986). *Uniroyal v. Rudkin-Wiley*, 5 U.S.P.Q.2d 1434, 1438 (Fed. Cir. 1988).

If motivation were to exist, which it does not, one would not be motivated to select specific characteristics of Ward and/or Heinsohn, Larsen, and Laustsen and use them in combination given their distinctly different purposes with the expectation that they would provide the method(s) of the claimed invention. Further, one would not be motivated to utilize the method of providing a polypeptide preparation comprising chymosin having a content of undesired enzymatic side activities selected from glucoamylase, peptidase, amylase, cellulase, phosphatase or protease at such a level that they do not restrict the applicability of said polypeptide preparation, particularly at a pH between about 1.5 and about 1.9. Indeed, the statutory standard of 35 U.S.C. §103 is whether the invention, considered as a whole, would have been obvious to one of ordinary skill in the art, not whether it would have been obvious for one of ordinary skill in the art to try various combinations. *Akzo N.V. v. E.I. duPont de Nemours*, 1 U.S.P.Q.2d 1705, 1707 (Fed. Cir. 1987). Where the prior art discloses no particular preference for the component claimed from among a number of other components disclosed in a reference, i.e., where there is no disclosure within the prior art that would have led the routineer to make the critical selections to arrive at the claimed composition, the Board found a rejection for obviousness could not be sustained. *Ex parte Wittpenn*, 16 U.S.P.Q.2d 1730, 1731 (BPAI 1990).

Each of the claims 2-6, 9-18, 29-31, 35-36 and 39-41 is dependent from claim 1, and therefore incorporates all of the limitations of claim 1 in addition to the further limitations set forth in the dependent claims at issue. As stated above, a proper *prima facie* obviousness rejection requires that the prior art reference(s) must teach or

suggest all of the claim limitations. For the reasons set forth above, Ward, Heinsohn, Larsen, and Laustsen do not render obvious the claims.

The references could have rendered Applicant's invention obvious only with the benefit of hindsight provided by Applicant's own disclosure. The use of hindsight is improper, as a matter of law, in considering non-obviousness of Applicant's claimed invention.

As stated in the M.P.E.P., "[i]f an independent claim is nonobvious under 35 U.S.C. § 103, then any claim depending therefrom is nonobvious." *See* M.P.E.P. § 2143.03 (citing *In re Fine*, 837 F.2d 1071, 5 U.S.P.Q.2d 1596 (Fed. Cir. 1988)).

For all the reasons discussed above, Applicant's claims are patentable in view of the references of record. Applicant has also filed a Declaration by a person skilled in the art which buttresses Applicant's contention of patentability of his claims. The rejection is respectfully traversed.

CONCLUSION

Applicant asserts that the application is in condition for allowance. Reconsideration and allowance of all pending claims is respectfully requested. Should any outstanding issues remain, the Examiner is invited to telephone the undersigned at 202-955-1926.

Respectfully submitted,

HUNTON & WILLIAMS

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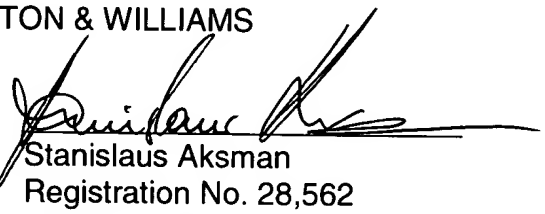
By: 

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